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Overview: Workshop on Fiber Toxicology Research Needs

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A great deal of toxicological and epidemiological data are available for asbestos and a wide variety of other mineral and manmade fibers. Experimental animal data suggest that certain fiber characteristics are responsible for observed biological effects such as cancer. An important fiber characteristic appears to be fiber size (length, diameter, aspect ratio); however, other characteristics such as *in vivo* persistence and durability, chemical composition, and surface chemistry (surface charge, etc.) may also be important, although less well studied.

Studies involving intrapleural or intraperitoneal implantation or injection have been most useful in determining fiber characteristics responsible for carcinogenic response; however, these studies may have limited utility in predicting actual human risks. Intrapleural models bypass normal lung defense mechanisms and related cell/fiber interactions. *In vivo* persistence, or the ability of the inhaled fiber to stay in the biological environment where introduced, is thought to be an important but not well-studied parameter that could explain the different responses seen by intrapleural versus inhalation studies.

Considerably more research is needed to more precisely identify mechanisms for fiber-induced disease and related fiber characteristics. To help define areas for further research, a workshop concerning "Fiber Toxicology Research Needs" sponsored by the National Institute of Environmental Health Sciences (NIEHS) was held in Research Triangle Park, NC from July 10 to 12, 1989. The workshop brought together international experts in environmental science, industrial hygiene, epidemiology, toxicology, and molecular biology. Objectives of the workshop were to critically review human and experimental data concerning fiber toxicology with an emphasis on biological mechanisms; identify data gaps and research needs; and suggest future research efforts.

In preparation for the workshop, critical review papers were prepared and distributed to conference participants. These review papers were presented and discussed during the first day of the workshop. During the second day participants were divided into four subgroups that addressed research needs in the areas of exposure assessment, *in vitro* studies, animal toxicology studies, and human epidemiology. The workshop's final day consisted of presentations and discussions of research recommendations developed during the four concurrent sessions.

The critical review papers are published in this volume. The following are reports from each of the subgroups.

Working Group Reports

Exposure Characterization

Current Issues. FIBER SAMPLING. One of the sampling methods currently used for the collection of fibrous aerosol samples in the workplace uses inlet cowls in conjunction with membrane filter sample holders. The use of a cowl was intended to enhance the uniformity of the distribution of the sample over the filter for increased accuracy of fiber counts. Among the problems with this method is the deposition of fibers on the cowl during field sampling. An additional extraction step that is involved in the resolution of the cowl deposition problem is expected to add to the sample variance, thus detracting from the accuracy of analysis. In addition, membrane filter sampling, with or without a cowl is designed to assess total suspended particulate matter (TSPM). Experience with fibers and other dusts has shown that TSPM measurements have a larger variance than measurements designed to estimate a subfraction of the airborne dust. In view of the biological effects of the fibrous dusts, the fraction of interest is related to fibers deposited in the alveolar and conducting airway compartments of the respiratory tract. Consequently, the use of size selective inlets such as thoracic particulate matter (TPM or PM-10) for fibrous aerosol sampling is recommended. The use of such inlets is expected

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to enhance the ease of microscopic analysis by the absence of extraneous particulate matter and fibers that either do not enter the human respiratory tract or deposit in the nasopharyngeal regions. Experience with the sampling of other particulate matter suggests that the use of such inlets results in a significant reduction in sample variance.

FIBER ANALYSIS. The use of indirect sample transfer for transmission electron microscopy (TEM) of asbestos has been shown to break up the airborne fibers into smaller units. Depending upon the treatment, the observed concentration of fibers and their size distribution change drastically. There is no biological justification for such a violent treatment, and the measured entity is not a biologically justifiable measured quantity. Therefore, the use of indirect sample transfer method for asbestos sampling should be discouraged, and the more gentle direct transfer method should be used.

DECISION TOOLS AND CONCENTRATION MEASURES. Clearly, the biological effects of fibers are related to their site of deposition, and there is evidence to suggest that different disease end points are related to different classes of fiber sizes and properties. The concentration estimates in both epidemiologic and toxicological studies should be based on a set of criteria related to the disease end points under consideration. This can be accomplished by the determination of concentration as a function of two-dimensional size distribution of fibers as well as other parameters related to disease outcome.

Recommendations. CHARACTERIZATION OF FIBERS IN TOXICOLOGICAL AND EPIDEMIOLOGIC STUDIES. The minimum exposure specification in epidemiologic and toxicological studies should include the identification of all fiber species present in the samples, identification and quantification of all other constituents, and a two-dimensional fiber size distribution, which would enable the exposure estimation to be carried out on a disease related basis such as the one proposed by Lippmann (*1*).

CREATION OF A REFERENCE LABORATORY FOR FIBERS. UICC samples that were prepared nearly 25 years ago have served their purpose admirably. However, in view of the subsequent developments in both physical and biological fields, the inadequacy of UICC samples are apparent.

A reference laboratory for fiber samples should be created. Such a reference laboratory would be a very important, perhaps essential, enhancement to future mechanistic research efforts. Functions of the laboratory are described below.

Repository for toxicological research fiber specimens. The purpose of the repository would be to prepare and hold reference material characterized in detail to be used in toxicological studies and to prepare fresh material if needed. The test materials should include all forms of asbestos in various stages of process (i.e., as mined, processed, etc.). Other natural minerals that are known to exist in fibrous habit such as erionite, sepiolite, attapulgite, etc., regional (e.g., Turkish and Oregon erionite), and processed (e.g., mined and processed attapulgite) specimens, nonfibrous analogues such as Riebeckite for crocidolite and manmade fibers of different manufacture and properties should be made available. These materials should be size classified with respect to appropriate parameters.

The samples should be classified with respect to as many parameters as feasible from the list suggested below. However, the two-dimensional size distribution of each sample, sample chemical constituents, comparative analysis with UICC samples (if applicable) should be a minimum level of information provided. Desirable information as requested by correspondents are: *a*) specific surface area; *b*) chemical composition; *c*) water, saline, and simulated lung fluid solubility; *d*) trace metal content, especially iron; *e*) trace organic content; *f*) surface charge at physiological pH (zeta potential); *g*) surface reactivity (ESR and spin trapping).

Repository for standardized specimens for analytical device calibration. For EM, XRF, EDXA, etc., calibration and sets of standardized specimens should be available.

Other functions. Other functions of the laboratory could include quality assurance, development and/or dissemination of appropriate image analysis software, workshops, and training.

Research Recommendations. The characterization of exposures in retrospective and prospective epidemiologic research involves a significant number of research problems that can be generalized in three categories: techniques for estimation of past exposures; reexamination of existing exposure data with respect to the development of process specific conversion factors between diverse exposure measurements and biologically based exposure indices; and development of sampling and analysis strategies for prospective epidemiologic studies.

The characterization of exposures in the toxicological research also involves a significant number of research problems that can be generalized in three categories: exposure delivery system; sampling and analytical methods; and preparation of samples that simulate various processes.

The specific research problems associated with the generalized research areas mentioned above would be too numerous to report and would in essence reflect the immediate interest of a very small fraction of researchers involved in the filed. We believe the response of the research community to these areas will provide a good list of specific research projects that would make significant contributions. There are, however, a few specific areas that should be highlighted to answer the immediate needs of the research community. These are discussed below.

Standard test material for *in vivo* and *in vitro* studies simulating industrial, mining, and end user processes/applications should be prepared to determine the essential differences in the biological response to these materials. Such preparation will involve the determination of the physical and chemical parameters of the

process-specific airborne dust and preparation of the test material that will simulate these parameters.

Related to this research area, as the process-specific physical and chemical parameters of the dust are determined, reconstruction of past exposures based on comparison of these parameters to existing historical exposure measurements or the estimation of past exposures based on these parameters may be carried out to explain some of the divergent results found in the epidemiologic studies.

Generation of fibrous aerosols requires review and possible development of new techniques. A number of techniques such as fluidized bed, vibrating bed, and grinder-type systems for introduction of fibers into animal exposure chambers are available. The modification of input dust parameters during the generation process, accumulation of electrical charges, etc., would be important in matching generation systems with the desired input material and the desired output.

Sampling techniques, size selective sampling, the efficiency of size selective inlets with respect to statistical considerations in counting and sizing require review and possible modification.

The two-dimensional size distribution analysis and the determination of a durability index of fibers require the development of a hierarchical sample analysis method. This can be accomplished by determining long fiber distribution in statistically significant numbers and short fiber distribution in a subset of the viewing fields in the same manner. Hierarchical methods that use variable magnification, matching of distributions, etc., should be investigated to facilitate the determination of two-dimensional size distributions.

There is sufficient evidence to suggest the importance of fiber durability in relation to disease outcomes. Consequently, development of a method for on-filter fiber durability measurement should also be investigated.

Aerodynamic factors as related to fiber shape are important in understanding the transport and deposition of fibers. Fundamental research on the aerodynamic behavior of straight versus curly fibers, fiber diffusion, etc., should be encouraged.

The size distribution of fibers that deposit in the lungs of experimental animals may be different from those that deposit in the lungs of humans. Mathematical models of particle deposition in human lungs have been described. These models are based upon aerodynamic behavior of particles, mechanics of respiration, and human lung architecture. Development of similar models for experimental animal species would help to define fiber sizes that can reach and deposit at specific sites in the test animal lungs. Research on the information needed for the development of such models should be encouraged.

In vivo alteration of fibers and its simulation will provide an important parameter of the experimental design. *In vivo* simulation of fiber alteration would involve coordinated toxicological and physicochemical research.

In addition to the eight research areas highlighted above, there is need for a certain amount of developmental work on analytical techniques for which much of the fundamental research exists. The following research items are related to making the analytical techniques more convenient: physical measurements of length, width, and surface area by view field scanning techniques; development of an approximate fiber durability index as a function of fiber solubility kinetics in body fluids; crystallographic measurements; and purity and/or impurity analysis.

In Vitro Studies on Fiber Toxicology

In vitro studies are important to understanding the mechanisms of fiber-induced inflammation, fibrosis, and neoplasia. Studies to establish the predictive value of *in vitro* assays for *in vivo* responses are needed. Several areas of future investigation were identified as important in achieving these goals. First, *in vitro* experiments to define the physicochemical characteristics of fibers involved in target cell interaction and injury are critical if *in vitro* models are to be used in predictive studies to assess the pathogenicity of substitutes for asbestos. Thus far, *in vitro* studies have supported animal and human data showing the importance of both fibrous geometry and longer, thinner fibers in the induction of cytotoxicity and lung disease. Clearly, additional studies are necessary to understand surface reactivity, chemistry, porosity, and other features of fibers that contribute to their pathogenicity. The development of a fiber repository to provide uniform, well-characterized preparations of fibers as well as particles (nonfibrous analogues) of identical chemical composition to cell biologists and toxicologists will be essential both to allow comparisons between laboratories and to address the issue of dosimetry at the cellular level. Most studies using fibers *in vitro* have in the past expressed dosage on the basis of fiber mass as opposed to numbers of fibers per cell, which now appears to be a more valid means of comparison of fiber effects in relation to their potential to cause human disease.

Studies comparing the kinetics of uptake of fibers in individual target cells of disease, i.e., mesothelial cell versus lung fibroblasts versus epithelial cells of the respiratory tract, would be useful in addressing whether processing fibers can be correlated with *in vitro* biological responses and the relative pathogenicity of these fibers *in vivo*. Analysis of the physicochemical properties of intracellular fibers will be important in determining how fibers are modified by the pulmonary environment. For example, an *in vitro* model simulating the formation of asbestos (ferruginous) bodies would provide valuable mechanistic information on the formation of these bodies in lung tissue. The issue of fiber durability and persistence in the lung may also be modeled in an *in vitro* system.

The development of well-defined *in vitro* lung cell systems to define components (serum factors, phospholipids, etc.) of lung microenvironment that might affect the biological activity of fibers is another research need. Maintenance of cells or co-cultures of target and effector

cells, i.e., alveolar macrophages, polymorphonuclear leukocytes, in chemically defined media should aid in studies to determine if cell-cell interactions are important in the elicitation and/or modulation of fiber-induced responses such as cytotoxicity, proliferation, and cytogenetic changes. Cross-species studies as well as comparisons between various lung cell types are needed to assess whether certain species and target cells of disease respond differently to various fibers. In these endeavors, comparison between the results of *in vitro* experiments and animal and human toxicity data should be encouraged in an attempt to identify the mechanisms responsible for human diseases induced by mineral fibers.

Several mechanistic studies should be addressed in an effort to understand the pathogenesis of fiber-induced malignancies. Development of mesothelial and tracheobronchial epithelial cell systems for demonstration of multistage fiber-induced carcinogenesis is necessary to address these fundamental questions: Is asbestos (or other asbestiform fibers) an initiator, promoter, or complete carcinogen in the development of mesothelioma versus bronchogenic carcinoma? Are there different mechanisms of fiber-induced carcinogenesis in the induction of these tumors? What is the role of other environmental pollutants, i.e., components of cigarette smoke, and endogenous host factors in initiation, promotion, and/or progression of mesothelioma and bronchogenic carcinoma?

In vitro experiments also should be designed to elucidate the cellular and molecular events involved in the process of carcinogenesis. These should include studies to evaluate fiber-induced DNA damage and repair in mesothelial/tracheobronchial epithelial cells, assessment of oncogene activation during initiation and promotion, loss of anti-oncogenes or tumor suppressor genes, induction of genes (antioxidant enzymes, etc.) involved in cell defense, and activation of genes linked to cell proliferation (ornithine decarboxylase, histones) and/or abnormal cell differentiation (keratin, collagen). Identification of novel or unique oncogenes associated with exposure of cells to carcinogenic fibers as well as studies to assess cooperation between oncogenes during cell transformation are fruitful areas of investigation. It will be important to examine both the mechanisms (i.e., active oxygen species, altered calcium metabolism) responsible for these alterations in gene expression as well as their relationship to the carcinogenic process.

The mechanisms of fiber-induced inflammation and its relationship to both carcinogenesis and nonmalignant respiratory disorders (pleural plaques, pulmonary interstitial fibrosis) also are enigmatic. The development of *in vitro* cell and multicell systems to define the physical/chemical properties of fibers that play a role in initiating the inflammatory process is necessary to elucidate the cell types, soluble mediators, and biological responses involved in fiber-induced inflammation. These experiments should evaluate the interactions between various cells of the immune system, i.e., neutrophils, subpopulations of lymphocytes, alveolar macrophages in various functional states, and the lung fibroblast.

The intracellular events resulting in activation of inflammatory and immune effector cells after exposure to asbestos and other asbestiform fibers are poorly understood. The possible role of surface receptors, second messenger pathways, and activation of specific genes (growth factors, cytokines) that may be involved in fiber-induced inflammatory and immune responses should be elucidated. A critical question to be addressed is how fibers elicit increased production of collagen and increased proliferation of lung parenchymal cells, events that occur during the fibrotic process. The quantitation and typing of collagen proteins and altered collagen gene expression in fibroblasts exposed to various fibers *in vitro* will be important in defining this process. The involvement of effector cells and growth factors in the elicitation and modulation of fiber-induced changes should also be examined. The types of information described above will be key to the identification and quantitation of reliable biomarkers that can be used *in vitro* and *in vivo* to effectively assess the pulmonary toxicity of fibers.

Defining the mechanisms of fiber-induced cell injury and altered cell proliferation is critical to modulation of these *in vitro* responses and will aid in the design of preventive/therapeutic approaches to disease. Cell culture and co-culture systems are necessary to evaluate immuno-modulating agents and anti-inflammatory drugs in the prevention of fiber-induced cell injury. Modulation of host defense systems by exogenous administration of antioxidants and anti-proteases are promising approaches that can be investigated using *in vitro* systems.

Toxicology

Measurement of Dose and Effects of Dose. A major failing of past experimental studies has been the use of mass as the main dose parameter. Data are needed on fiber comparison by fiber number. In this context, important decisions must be made on the dimensions of fibers used for comparison purposes and methods of estimation (e.g., TEM). If possible, experimental exposures should be the same range of fiber dimensions as those found for human exposure in the industrial environment. However, for examining the carcinogenic or fibrogenic potency of certain fiber dimensions, special samples with suitable particle size dimensions should be used. The duration and continuity of exposure are of great importance and must be matched if meaningful comparisons with other studies are to be made.

Information is needed on the relationship between dose inhaled and dose received in and retained in the lung parenchyma. Consequently, all studies should include both forms of dust estimation.

The concept of fiber durability is frequently mentioned in relation to pathogenicity. Durability in the lung needs to be examined in detail for a selected range of fibers. As part of this work checks must be under-

taken that methods of dust extraction from lung tissue do not change fiber dimensions.

The importance of fiber dimension (long, thin fibers) has been recognized for many years. Other physical factors may also be important (e.g., surface area and surface chemistry) and should be examined. The porous surface of erionite is an example of a factor that may be important.

Evidence is needed on the effects of excessive or overload doses in experimental studies on the ability to predict human hazard. There is evidence that excessive dose levels produce pulmonary pathology with almost any material. As the same time, low exposure levels may not demonstrate a hazard in short-lived animals. Selection of the best intermediate dose is most important.

More than 95% of human lung cancers originate in the bronchial wall, but nearly all asbestos fibers found in the lung are retained in the unciliated airways or interstitium. It should be clarified whether the low number of those fibers that are lodging in the bronchial wall are responsible for tumor induction or the much higher number of fibers retained in the alveoli and the interstitium.

Carcinogenic Factors and Site of Tumor Formation. Information is still needed on whether the physical or chemical parameters responsible for pulmonary carcinogens are the same as those effective in producing mesotheliomas. Part of this problem is the consideration of whether those physical and chemical properties have their effects on mesothelioma production by effecting the rate of fiber transport to the pleura. Evidence for or against a threshold dose for fiber carcinogenicity is still required.

Importance of Fibrosis. AS A DISEASE ENTITY ON ITS OWN. It is believed that the major emphasis of fiber research relates to tumor production but that pulmonary fibrosis remains a potential hazard and fibrogenic mechanisms still need elucidation. Studies are needed to investigate pathogenetic mechanisms of fiber-induced pulomonary fibrosis. These should include investigations into early cellular mechanisms of fibrosis; identification of target cells in the distal lung; and clarification of the complex interactions in the interstitial microenvironment between effector cells and target cells, as well as the role of mediators and mitogenic factors regulating (both up and/or down) the proliferative responses of pulmonary fibroblasts.

It is also believed that present methods of quantifying fibrosis are inadequate. Standard light and electron microscopic morphometric techniques should be developed to obtain an objective measure of pulmonary fibrosis.

AS AN ELEMENT IN TUMOR PRODUCTION. The relationship between pulmonary fibrous and pulmonary tumors and also pleural fibrosis and mesothelioma is still uncertain and needs further examination.

Importance of the Interaction of Fibers with Other Carcinogenic Agents. More information is needed on the importance of the interaction of fibers with other carcinogenic agents in general. In particular, the synergistic relationship demonstrated between asbestos and cigarette smoke should be examined with other fiber types.

Validation of Assay Methods. There is a great need for the validation of *in vitro* assays, short-term inhalation assays, and noninhalation *in vivo* studies as predictors (qualitative and quantitative) of responses observed in laboratory animals and people exposed to fibers via inhalation.

There is a need for long-term studies in laboratory animals using multiple levels to examine the development of the diseases of interest (lung cancer, mesothelioma, and fibrosis). This can be accomplished if a few well-characterized fiber preparations are used for long-term laboratory animal inhalation studies, *in vitro* investigations, and laboratory animal studies using noninhalation methods of fiber administration.

Human Epidemiology

The Human Epidemiology Group discussed research priorities in relation to assessment of exposure and assessment of health effects. Interpretation of epidemiological studies of asbestos-exposed populations has been greatly handicapped by less than adequate assessment of exposure and must be improved in subsequent studies if the many lessons on fiber toxicity taught to us by asbestos are to be fully realized. At the present time, lack of adequate exposure assessment has led to a lack of precision and quantification in understanding health effects risks for industrial application of asbestos by fiber type.

Exposure Assessment in Studies of Health Effects. All epidemiological studies should seek to quantify prospectively and retrospectively, to the extent possible, fiber characteristics by type and dimensions most relevant for biological effect as described by Lippmann (*1*).

Confounding occupational exposures such as other particulate exposures in the manmade mineral fiber industry are of potential importance in defining dose-response relationships and should be defined and measured whenever possible.

The role of smoking in regard to lung cancer risk is generally well understood, but the risk of nonsmokers who are exposed to fibers could be further defined. Assessments of exposures and health effects in the construction trades are needed to further understand risk.

Studies of exposures and health effects related to tremolite and amphibole-contaminated vermiculite and talc in all stages of use [e.g., mining and milling, expansion plants (vermiculite), end use manufacturing, and consumer use] are a priority.

Exposure and health effects studies of nonasbestiform silicates such as wollastonite and attapulgite (with potential large populations at risk) are needed.

Assessment of exposures and health effects of small diameter manmade mineral fibers (MMMF), ceramic fibers and other long, thin, durable MMMF is a priority.

Studies of fiber burden within the human lung by fiber

type, dimension, solubility/durability are needed to allow understanding of pulmonary pathology data.

Health Effects. Several epidemiological study designs were discussed as priorities for research. Conversion of morbidity studies into mortality studies with prospective follow-up offers advantages in terms of definition of risk factors and antecedent health effects and should be given priority.

The use of nested case-control studies with defined cohorts reduces selection bias yet offers an opportunity to further assess exposures through follow-back studies and assessment of lung fiber burden.

Systematic national surveillance for mesothelioma with further attention to diagnosis and follow-back for relevant occupational and/or environmental exposure is needed.

Use of radiographic techniques of high resolution computerized tomography (CT) holds promise for definition, standardization, and assessment of pleural disease in relation to impairment. Thin section CT scans can provide an opportunity to further define small opacities in living subjects to more fully understand their etiology and relation to impairment. The application of these tools to well-defined populations is needed.

Further studies are needed concerning the importance of pulmonary fibrosis (both parenchymal and pleural) from fiber and nonfiber etiologies and the role of fibrosis in human carcinogenesis.

APPENDIX

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